OPIC
OFFICE DE LA PROPRIÉTÉ INTELLECTUELLE DU CANADA

CIPO
CANADIAN INTELLECTUAL PROPERTY OFFICE

Ottawa Hull K1A 0C9

(21) (A1) 2,108,899
(88) 1992/03/13
(43) 1992/09/16

(51) INTL.CL.[5] C07D-498/04; C07D-487/04; A61K-031/395

(19)(CA) **APPLICATION FOR CANADIAN PATENT** (12)

(54) Use of Oxazolo-[2,3-a]-Isoindole and Imidazo-[2,1-a]-Isoindole Derivatives as Antiviral Medicaments, as Well as New Oxazolo-[2,3-a]-Isoindole Derivatives

(72) König, Bernhard - Germany (Federal Republic of) ;
Leser, Ulrike - Germany (Federal Republic of) ;
Mertens, Alfred - Germany (Federal Republic of) ;
Schäfer, Wolfgang - Germany (Federal Republic of) ;
Poll, Thomas - Germany (Federal Republic of) ;

(71) Boehringer Mannheim GmbH - Germany (Federal Republic of) ;

(30) (DE) P 41 08 395.4 1991/03/15

(57) 9 Claims

PCT WELTORGANISATION FÜR GEISTIGES EIGENTUM
Internationales Büro
INTERNATIONALE ANMELDUNG VERÖFFENTLICHT NACH DEM VERTRAG ÜBER DIE INTERNATIONALE ZUSAMMENARBEIT AUF DEM GEBIET DES PATENTWESENS (PCT)

(51) Internationale Patentklassifikation 5 :
A61K 31/415, 31/42
C07D 487/04, 498/04 // (C07D 487/04 C07D 235:00, 209:00) (C07D 498/04, 263:00, 209:00)

A1

(11) Internationale Veröffentlichungsnummer: WO 92/16207

(43) Internationales Veröffentlichungsdatum: 1. Oktober 1992 (01.10.92)

(21) Internationales Aktenzeichen: PCT/EP92/00558

(22) Internationales Anmeldedatum: 13. März 1992 (13.03.92)

(30) Prioritätsdaten:
P 41 08 395.4 15. März 1991 (15.03.91) DE

(71) Anmelder *(für alle Bestimmungsstaaten ausser US)*: BOEHRINGER MANNHEIM GMBH [DE/DE]; Sandhoferstr. 116, D-6800 Mannheim 31 (DE).

(72) Erfinder; und
(75) Erfinder/Anmelder *(nur für US)* : KÖNIG, Bernhard [DE/DE]; Dürrbergstr. 28, D-8137 Berg (DE). LESER, Ulrike [DE/DE]; Stiftsbogen 64, D-8000 München 70 (DE). MERTENS, Alfred [DE/DE]; Beethovenstr. 20, D-6905 Schriesheim (DE). SCHÄFER, Wolfgang [DE/DE]; Feldbergstr. 60, D-6800 Mannheim 1 (DE). POLL, Thomas [DE/DE]; Gambrinusstr. 4 A, D-6800 Mannheim 31 (DE).

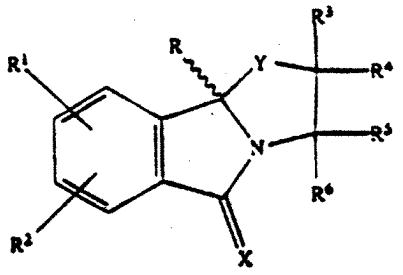
(74) Anwälte: WEBER, Manfred usw. ; Boehringer Mannheim GmbH, Sandhoferstr. 116, D-6800 Mannheim 31 (DE).

(81) Bestimmungsstaaten: AT (europäisches Patent), AU, BE (europäisches Patent), BG, BR, CA, CH (europäisches Patent), CS, DE (europäisches Patent), DK (europäisches Patent), ES (europäisches Patent), FI, FR (europäisches Patent), GB (europäisches Patent), GR (europäisches Patent), HU, IT (europäisches Patent), JP, KR, LU (europäisches Patent), MC (europäisches Patent), NL (europäisches Patent), NO, PL, RO, RU, SE (europäisches Patent), US.

Veröffentlicht
Mit internationalem Recherchenbericht.

(54) Title: USE OF OXAZOLO-[2,3-a]ISOINDOLE AND IMIDAZO[2,1-a]ISOINDOLE DERIVATIVES AS ANTIVIRAL DRUGS, AND NEW OXAZOLO[2,3-a]ISOINDOLE DERIVATIVES

(54) Bezeichnung: VERWENDUNG VON OXAZOLO-[2,3-a]ISOINDOL- UND IMIDAZO[2,1-a]ISOINDOL-DERIVATEN ALS ANTIVIRALE ARZNEIMITTEL SOWIE NEUE OXAZOLO[2,3-a]ISOINDOL-DERIVATEN



(I)

(57) Abstract

The invention concerns the use of oxazolo-[2,3-a]isoindole and iminazo[2,1-a]isoindole derivatives as antiviral drugs, as well as optically active derivatives, new oxazolo-[2,3-a]isoindole derivatives, a method for preparing them and drugs containing these compounds. In particular, the subject matter of the invention is the use of oxazolo-[2,3-a]isoindole and imidazo[2,1-a]isoindole derivatives of general formula (I) to produce antiviral drugs. In formula (I), X stands for an oxygen atom or a sulphur atom, the imino group =NH or a $=N\text{-}C_1\text{-}C_5$ alkylimino group, Y stands for an oxygen atom or the group NR^7, wherein R^7 is a hydrogen atom or a $C_1\text{-}C_6$ alkyl residue or a $C_1\text{-}C_6$ acyl residue, R is a hydrogen atom, a straight-chain or branched, saturated or unsaturated aliphataic residue containing 1-9 carbon atoms, possibly substituted by phenyl, or a phenyl ring possibly substituted one or more times, or a carbocyclic or heterocyclic ring, R^1 and R^2 stand for a hydrogen atom, a straight-chain or branched, saturated or unsaturated aliphatic residue with 1 to 6 carbon atoms, $R^3\text{-}R^6$ stand for hydrogen, $C_1\text{-}C_6$ alkyl, $C_1\text{-}C_6$ alkoxy, $C_1\text{-}C_6$ alkylmercapto, amino, $C_1\text{-}C_6$ alkylamino, di-$C_1\text{-}C_6$ alkylamino, halogen, cyano, hydroxy, carboxy, aminocarbonyl, substituted aminocarbonyl or $C_1\text{-}C_6$ alkoxycarbonyl. The invention also concerns their tautomers, enantiomers, diastereomers and physiologically acceptable salts.

Boehringer Mannheim GmbH 3477/00/

Use of oxazolo-/2,3-a/-isoindole and imidazo-/2,1-a/-isoindole derivatives as antiviral medicaments, as well as new oxazolo-/2,3-a/-isoindole derivatives

The present invention concerns the use of oxazolo-/2,3-a/-isoindole and imidazo-/2,1-a/-isoindole derivatives as antiviral medicaments, as well as new optically-active derivatives and new oxazolo-/2,3-a/-isoindole derivatives, processes for their preparation and medicaments which contain these compounds.

The use of oxazolo-/2,3-a/-isoindole and imidazo-/2,1-a/-isoindole derivatives as medicaments is described in several publications. Thus, derivatives of these substance classes are described in J. Org. Chem. 55, 3088, 1990, as inhibitors of gamma-butyrobetaine hydroxylase. Furthermore, the following pharmacological actions are described:

a) appetite suppressor action in US 3,994,920 and US 3,935,218,

b) treatment of gastritis in US 3,966,955,

c) anti-depressive action in US 3,935,219, US 3,900,494, US 3,898,226, US 3,898,231, US 3,885,037, US 3,867,394, US 3,867,394 and US 3,763,178,

d) diuretic action in US 3,935,218, US 3,898,226, US 3,898,231, US 3,885,037 and US 3,867,394,

e) anti-hyperglycaemic action in US 3,928,597,

f) anorexic action in US 3,898,226, US 3,898,231 and US 3,885,037,

g) anti-inflammatory action in CH 480350 and US 3,408,350,

h) analgesic action in CH 480,350, CH 482,697, CH 481,124 and CH 481,123,

i) blood pressure-sinking action in CH 480,350, CH 481,124 and CH 481,123,

j) spasmolytic action in CH 480,350, CH 481,124 and CH 481,123,

k) tranquiliser and sedative action in CH 480,350 and CH 481,123,

l) antitussive action in CH 480,350, CH 481,124 and CH 481,123 and

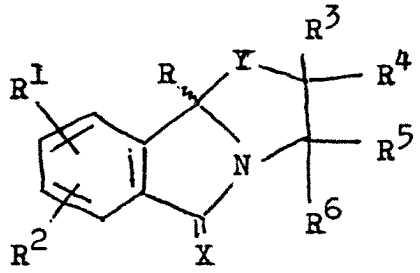
m) rheumatic action in CH 482,697.

The oxazolo-/2,3-a/-isoindole and imidazo-/2,1-a/-isoindole derivatives of the general formula I also possess, in part, a certain potential as intermediate products for the preparation of structurally similar classes of compounds. These intermediate products are described in CS 201,499; Aust. J. Chem., 35, 2307, 1982; US 4,018,765; GB 1,225,411; US 3,925,359; US 3,929,766; US 3,910,947; US 3,905,994; J. Med. Chem. 18, 177, 1975; J. Org. Chem. 40, 382,1975; DE 1,795,785; GB 1,322,339; US 3,663,532; GB 1,258,946; FR 7457; DE 2,106,694; GB 1,225,411; GB 1,232,469; GB 1,225,413; FR 1,580,180; FR 1,580,184, FR 1,571,331; US 3,454,592;

US 3,441,572; SA 6,801,724; J. Org. Chem. 34, 1720, 1969; SA 6,801,872; US 3,379,733.

The synthesis of the compounds of the general formula I is described, inter alia, in J. Heterocycl. Chem. 26, 1441, 1989; Gazz. Chim. Ital. 155 (12, part B), 653, 1985; Bull. Soc. Chim. Belg. 95, 197, 1986; J. Chem. Soc., Perkin Trans. 1, 809, 1985; J. Org. Chem., 45, 4049, 1980; US 3,867,401; DE 2,332,232; US 3,657,221; US 3,507,863; GB 1,059,175; J. Org. Chem. 34, 165, 1969; US 3,403,164; J. Org. Chem. 33, 2874, 1968; US 3,336,306; US 3,334113; NL 6,613,264; J. Org. Chem. 32, 2180, 1967; J. Org. Chem. 32, 2185,1967 and Belg. 659,530.

The invention concerns the use of oxazolo-[2,3-a]-isoindole and imidazo-[2,1-a]-isoindole derivatives of the general formula I



(I)

for the preparation of medicaments with antiviral action, whereby X can be an oxygen or sulphur atom, the imino group =NH or an $=N-C_1-C_5$-alkylimino group, Y can be an oxygen atom or the group NR^7, whereby R^7 signifies a hydrogen atom or a C_1-C_6-alkyl or C_1-C_6-acyl radical, R signifies a hydrogen atom, a straight-chained or branched, saturated or unsaturated

aliphatic radical with 1 - 9 C-atoms, which can be substituted by phenyl, or a C_1-C_6-alkoxy-C_1-C_6-alkyl or C_1-C_6-alkylmercapto-C_1-C_6-alkyl radical, or signifies a phenyl ring which is possibly substituted one or more times by C_1-C_6-alkyl, C_1-C_6-alkoxy, C_1-C_6-alkylmercapto, C_1-C_6-alkylsulphinyl, C_1-C_6-alkylsulphonyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl, C_2-C_6-alkenyloxy, C_2-C_6-alkenylmercapto, C_2-C_6-alkynyloxy, C_2-C_6alkynylmercapto, amino, C_1-C_6-alkylamino, di-C_1-C_6-alkylamino, C_1-C_6-alkylcarbonylamino, C_1-C_6-alkylaminocarbonyl, C_1-C_6-alkoxycarbonyl, hydroxyl, benzyloxy, phenylmercapto, phenyloxy, nitro, cyano, halogen, trifluoromethyl, azido, formylamino, carboxyl or phenyl, or signifies a mono-, bi- or tricyclic carbocyclic ring with 7 - 15 C-atoms or a heterocyclic mono-, bi- or tricyclic ring system with, in each case, 5 or 6 ring atoms and, per ring system, can contain 1 - 4 or 1 - 5 heteroatoms, respectively, whereby the heteroatoms are nitrogen, sulphur or oxygen, R^1 signifies a hydrogen atom, a straight-chained or branched, saturated or unsaturated aliphatic radical with 1 - 6 C-atoms or C_1-C_6-alkoxy, C_1-C_6-alkylmercapto, C_1-C_6-alkylsulphonyl, C_1-C_6-alkylsulphonyl, amino, C_1-C_6-alkylamino, di-C_1-C_6-alkylamino, sulphonamido, C_1-C_6-alkoxycarbonyl, trifluoromethyl, carboxyl, halogen, hydroxyl, nitro, cyano, azido, phenyl or benzyloxy, R^2 has the same meaning as R^1, whereby the radicals R^1 and R^2, independently of one another, can

be the same or different, R^3 signifies hydrogen, C_1-C_6-alkyl, C_1-C_6-alkoxy, C_1-C_6-alkylmercapto, amino, C_1-C_6-alkylamino, di-C_1-C_6-alkylamino, halogen, cyano, hydroxyl, carboxyl, C_1-C_6-alkoxycarbonyl, aminocarbonyl, C_1-C_6-alkylaminocarbonyl or di-C_1-C_6-alkylaminocarbonyl, R^4, R^5, R^6 have the same meaning as R^3, whereby the radicals R^3, R^4, R^5 and R^6, independently of one another, can be the same or different, as well as their tautomers, enantiomers, diastereomers and physiologically compatible salts.

For the case that Y is an oxygen atom and R^1 and R^2 do not simultaneously signify hydrogen atoms, it is a question of new oxazolo-[2,3-a]-isoindole derivatives which are also the subject of the present invention.

The compounds of the formula I have hitherto only been known in the form of their racemates. It has now been shown that the optically-active derivatives possess a higher effectiveness than the corresponding racemic mixtures so that the present invention also refers to the the new R- and S-enantiomers.

The compounds of the formula I display valuable pharmacological properties. In particular, they are suitable for the therapy and prophylaxis of infections which are caused by DNA viruses, such as e.g. herpes simplex virus, cytomegalovirus, papillomaviruses, the varicella zoster virus or Epstein-Barr virus or RNA viruses, such as togaviruses or especially retroviruses, such as the oncoviruses HTLV-I and II, as

well as the lentiviruses visna and human immune deficiency virus HIV-1 and -2.

The compounds of the formula I appear to be especially suitable for the treatment of the clinical manifestations of the retroviral HIV infection in humans, as well as of the persistent general lymphadenopathy (PGL), the advanced stage of the AIDS-related complex (ARC) and the clinically complete picture of AIDS.

The compounds of the general formula I possess an outstanding antiviral action and are especially suitable for the treatment of viral or retroviral infections. Viral infections of mammals, especially of humans, are wide spread. In spite of intensive efforts, it has hitherto not been successful to make available chemotherapeutics which interfere causally or symptomatically with the virally or retrovirally caused appearances of diseases with recognisable substantial success. At present, it is not possible to cure certain viral diseases, such as for example the acquired immune deficiency syndrome (AIDS), the AIDS-related complex (ARC) and their preliminary stages, herpes, cytomegalovirus (CMV), influenza and other virus infections or chemotherapeutically favourably to influence their symptoms. At present, for example, for the treatment of AIDS there is available almost exclusively 3'-azido-3'-deoxythymidine (AZT), known as Zidovudine or Retrovir^{R}.

However, AZT is characterised by a very narrow therapeutic spectrum or by very severe toxicities already appearing in the therapeutic range (Hirsch, M.S. (1988) J. Infec. Dis. 157, 427-431). The compounds of the general formula I do not possess these disadvantages. They act antivirally without being cytotoxic in pharmacologically relevant doses.

It could now be demonstrated that compounds of the general formula I inhibit the multiplication of of DNA and RNA viruses, respectively, at the stage of the virus-specific DNA and RNA transcription, respectively. Via the inhibition of the enzyme reverse transcriptase, the substances can influence the multiplication of retroviruses (cf. Proc. Natl. Acad. Sci. USA 83, 1911, 1986 or Nature 325, 773, 1987).

Since a very great need exists for chemotherapeutics which interfere as specifically as possible with retrovirally-caused diseases or their symptoms without influencing the normally occurring natural body functions, the said compounds could be advantageously used prophylactically or therapeutically in the treatment of diseases in which a retroviral infection is of pathophysiological, symptomatic or clinical relevance.

The separation of the racemates into the enantiomers can be carried out analytically, semipreparatively and preparatively chromatographically on suitable optically-active phases with usual elutions agents.

As optically-active phases, there are suitable, for example, optically-active polyacrylamides or polymethacrylamides, in some cases also on silica gel (e.g. ChiraSpher (R) of Merck, Chiralpak (R) OT/OP of Baker), cellulose esters/carbamates (e.g. Chiracel (R) OB/OY of Baker/Daicel), phases based on cyclodextrin or crown ethers (e.g. Crownpak (R) of Daicel) or microcrystalline cellulose triacetate (Merck).

An aliphatic radical means a straight-chained or branched alkyl, alkenyl or alkynyl radical with 1 - 9, preferably 2 - 7 carbon atoms, such as e.g. the propyl, isopropyl, butyl, isobutyl, pentyl, hexyl or heptyl radical. As unsaturated radicals, there come into question C_2-C_7-alkenyl and alkynyl radicals, preferably C_2-C_5, such as e.g. allyl, dimethylallyl, butenyl, isobutenyl, pentenyl or propynyl radical.

An aliphatic radical which can be substituted by phenyl is especially a phenyl-C_1-C_6-alkyl group, such as e.g. the benzyl, phenethyl, phenylpropyl or phenylbutyl radical.

If R signifies a phenyl ring, this can be substituted one, two or three times. Independently of one another, the substituents can stand in the o-, m- or p-position.

A carbocyclic ring with 7 - 15 C-atoms can be mono-, bi- or tricyclic and, per ring, can, in each case, have 5 or 6 C-atoms. This ring can be saturated, unsaturated, partly saturated or aromatic. By way of

example are mentioned the following ring systems: the naphthyl, anthracenyl, phenanthrenyl, fluorenyl, indenyl, indanyl, acenaphthylenyl, norbornyl, adamantyl ring or C_3-C_7-cycloalkyl or C_5-C_8-cycloalkenyl group.

The heterocyclic mono-, bi- or tricyclic ring systems contain, per ring system, 5 or 6 carbon atoms, whereby 1 - 4 or 1 - 5 C-atoms, respectively, can be replaced by the heteroatoms oxygen, sulphur and/or nitrogen. The ring systems can be aromatic, partly or completely hydrogenated. The following ring systems can be mentioned by way of example: the pyridine, pyrimidine, pyridazine, pyrazine, triazine, pyrrole, pyrazole, imidazole, triazole, thiazole, oxazole, isoxazole, oxadiazole, furazane, furan, thiophene, indole, quinoline, isoquinoline, cumarone, thionaphthene, benzoxazole, benzthiazole, indazole, benzimidazole, benztriazole, chromene, phthalazine, quinazoline, quinoxaline, methylenedioxybenzene, carbazole, acridine, phenoxazine, phenothiazine, phenazine or purine system, whereby the unsaturated or aromatic carbo- or heterocycles can be partly or completely hydrogenated.

R preferably signifies unsubstituted phenyl or phenyl substituted once or twice by C_1-C_6-alkyl, C_1-C_6-alkoxy, C_1-C_6-alkylmercapto, C_1-C_6-alkylsulphinyl, C_1-C_6-alkylsulphonyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl, C_3-C_6-alkenyloxy, C_1-C_6-alkylamino,

C_1-C_6-dialkylamino, C_1-C_6-alkylcarbonylamino, C_1-C_6-alkylaminocarbonyl, C_1-C_6-alkoxycarbonyl, amino, hydroxyl, nitro, azido, trifluoromethyl, cyano or halogen. The previously mentioned "alkyl" parts preferably contain in the definitions in question up to 4, especially up to 3 C-atoms.

Carbocyclic rings are preferably biphenyl, naphthyl, anthracenyl, indenyl, fluorenyl, acenaphthylenyl, phenanthrenyl, norbornyl, adamantyl, C_3-C_6-cycloalkyl, C_5-C_8-cycloalkenyl.

Heterocyclic ring systems are preferably pyrrole, imidazole, furan, thiophene, pyridine, pyrimidine, thiazole, triazine, indole, quinoline, isoquinoline, cumarone, thionaphthene, benzimidazole, quinazoline, methylenedioxybenzene, ethylenedioxybenzene, carbazole, acridine and phenothiazine.

For the radicals R^1 and R^2 are preferred hydrogen, C_1-C_6-alkyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl, C_1-C_6-alkoxy, C_1-C_6-alkylmercapto, C_1-C_6-alkylamino, C_1-C_6-alkoxycarbonyl, trifluoromethyl, amino, halogen, hydroxyl, cyano and azido, whereby the "alkyl" parts in the previously mentioned definitions preferably contain up to 4, especially up to 3 C-atoms.

Preferred substituents for R^3, R^4, R^5 and R^6 are hydrogen, C_1-C_6-alkyl, C_1-C_6-alkoxy, C_1-C_6-alkylmercapto, carboxyl, C_1-C_6-alkoxycarbonyl, halogen, cyano and hydroxyl, whereby the "alkyl" parts in the

previously mentioned definitions preferably contain up to 4, especially up to 3 C-atoms.

X is preferably oxygen or sulphur. By halogen is generally to be understood fluorine, chlorine, bromine and iodine, preferably fluorine, chlorine and bromine.

Y is preferably oxygen or $-NR^7$, whereby for R^7 there comes into question hydrogen or the C_1-C_6-alkyl or C_1-C_6-acyl radical. By acyl radical, one understands especially the C_1-C_6-alkylcarbonyl radical. The "alkyl" parts preferably contain up to 4, especially up to 3 C-atoms.

Especially preferred radicals for R are C_3-C_5-alkyl, phenyl, phenyl mono- or disubstituted by C_1-C_6-alkyl, C_1-C_6-alkoxy, trifluoromethyl or halogen, naphthyl, anthracenyl, indanyl, furyl, thienyl, pyridyl, indolyl, quinolinyl.

For R^1 and R^2, independently of one another, there are especially preferred hydrogen, methyl, ethyl, isopropyl, trifluoromethyl, methoxy, ethoxy and halogen, whereby chlorine and bromine are especially preferred for halogen.

For R^3, R^4, R^5 and R^6, aminocarbonyl, methyl, ethyl and isopropyl are especially preferred.

Especially preferred are compounds of the general formula I in which R, R^1, X and Y have the above-given meaning and R^2, R^3, R^4, R^5 and R^6 are equal to hydrogen, methyl, ethyl, chlorine, bromine, methoxy

or ethoxy, whereby R^2 to R^6 above all represent hydrogen.

The medicaments containing at least one compound of the formula I for the treatment of viral or retroviral infections or of diseases caused by these can be administered enterally or parenterally in liquid or solid form. There hereby come into question the usual forms of administration, such as for example tablets, capsules, dragees, syrups, solutions or suspensions. As injection medium, water is preferably used which contains the additives usual in the case of injection solutions, such as stabilising agents, solubilising agents and buffers. Such additives are e.g. tartrate and citrate buffers, ethanol, complex formers, such as ethylenediamine-tetraacetic acid and its non-toxic salts, high molecular polymers, such as liquid polyethylene oxide, for viscosity regulation. Liquid carrier materials for injection solutions must be sterile and are preferably filled into ampoules. Solid carrier materials are, for example, starch, lactose, mannitol, methyl cellulose, talc, highly dispersed silicic acids, high molecular fatty acids, such as stearic acid, gelatine, agar-agar, calcium phosphate, magnesium stearate, animal and vegetable fats, solid high molecular polymers, such as polyethylene glycol, etc. Compositions suitable for oral administration can, if desired, contain flavouring or sweetening materials.

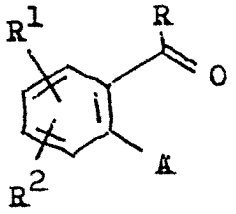
For the preparation of physiologically compatible salts, compounds of the formula I, which carry a basic group, are reacted with inorganic or organic acids, such as e.g. with hydrochloric acid, hydrobromic acid, sulphuric acid, phosphoric acid, fumaric acid, succinic acid, tartaric acid, citric acid, lactic acid or maleic acid, and the acid-addition salts isolated. If the compounds of the formula I contain an acid group, then one obtains the physiologically compatible salts by reaction with alkali metal or alkaline earth metal hydroxide, such as e.g. sodium hydroxide, potassium hydroxide or calcium hydroxide, or with other basic groups, such as amines, e.g. triethylamine.

The dosaging can depend upon various factors, such as mode of administration, species, age or individual state of health. The compounds according to the invention are usually administered in amounts of 0.1 - 100 mg, preferably of 0.2 - 80 mg per day and per kg of body weight. It is preferred to divide up the daily dose into 2 - 5 administrations, whereby, in the case of each administration, 1 - 2 tablets with an active material content of 0.5 - 500 mg are administered. The tablets can also be retarded, whereby the number of administrations per day is reduced to 1 - 3. The active material content of the retarded tablets can amount to 2 - 1000 mg. The active material can also be given by continuous infusion,

whereby the amounts of 5 - 1000 mg per day normally suffice.

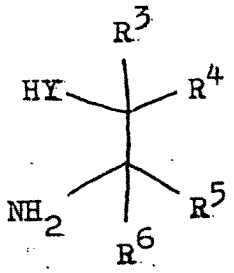
The medicaments containing at least one compound of the formula I are prepared in that one mixes a compound of the formula I with usual pharmaceutical adjuvants and works up to medicinal forms, such as e.g. tablets, dragees, capsules or solutions. These medicinal forms are made up into packaging units ready for sale and provided with an appropriate instruction, e.g. in the form of a packaging leaflet or printed instructions on the packaging from which follows the use for the treatment of viral or retroviral infections or of diseases caused by these infections.

The compounds of the general formula I according to the invention are prepared according to processes known from the literature in that one reacts possibly substituted benzoic acid derivatives of the general formula II



(II),

in which R, R^1 and R^2 have the above-given meaning and A is equal to -COOH or C=N, with substituted or unsubstituted ethanolamine or ethylenediamine of the general formula III



(III),

in which Y, R^3, R^4, R^5 and R^6 have the given meaning, in a suitable inert solvent at room temperature to reflux temperature, possibly in the presence of catalytical amounts of acid, e.g. p-toluenesulphonic acid, and possibly subsequently converts compounds of the formula I into other compounds of the formula I and subsequently purifies chromatographically or by recrystallisation. Racemates can be separated into the antipodes by chromatography on suitable optically-active phases, e.g. cellulose triacetate.

The subsequent conversion of compounds of the formula I into other compounds of the formula I concerns the preparation of oxazolo-/2,3-a/isoindole or imidazo-/2,1-a/-isoindole derivatives with X = S or N-alkylimine. Compounds with X = S are prepared by reaction of compounds of the formula I, in which X signifies an oxygen atom, with sulphur group-transferring compounds, such as e.g. Lawesson's reagent. Compounds with X = N-alkylimino are prepared by reaction of the corresponding imino compounds of the general formula I with alkylamines according to per se known methods.

The benzoic acid derivatives of the general formula II are also known from the literature and are prepared e.g. by Friedel-Crafts acylation of substituted or unsubstituted phthalic acid anhydride with possibly substituted arenes in the presence of a Lewis acid (e.g. aluminium chloride) or by reaction of Grignard reagents of the general formula IV

$$R\text{-}MgBr \qquad (IV),$$

in which R, with the exception of hydrogen, has the above-given meaning, with phthalic acid anhydride, which is possibly substituted, in suitable inert solvents at low temperatures.

The processes for the preparation of the compounds of the general formula I according to the invention can also be taken from the patent applications or literature references given in the prior art.

In the meaning of the present invention, apart from the compounds mentioned in the Examples and those given by combination of all meanings of the substituents mentioned in the claims, the following compounds of the formula I come into question which can be present as racemic mixture or in optically-active form or as pure R- and S-enantiomers.

Compounds of the formula I, in which Y signifies an oxygen atom are especially the following:

1. 8,9b-dimethyl-2,3-dihydrooxazolo-[2,3-a]-isoindol-5(9bH)-one

2. 8-chloro-9b-phenyl-2,3-dihydrooxazolo-[2,3-a]-isoindol-5(9bH)-one

3. 8-fluoro-9b-(4-methylphenyl)-2,3-dihydrooxazolo-[2,3-a]-isoindol-59(bH)-one

4. 8-chloro-9b-(3-methylphenyl)-2,3-dihydrooxazolo-[2,3-a]-isoindol-5(9bH)-one

5. 3-methyl-9b-(4-ethylphenyl)-2,3-dihydrooxazolo-[2,3-a]-isoindol-5(9bH)-one

6. 9b-(2,3-dimethylphenyl)-2,3-dihydrooxazolo-[2,3-a]-isoindole-5(9bH)-thione

7. 8-chloro-9b-(3,4-dimethylphenyl)-2,3-dihydro-oxazolo-[2,3-a]-isoindole-5(9bH)-thione

8. 2-ethyl-9b-(2,5-dimethylphenyl)-2,3-dihydrooxazolo-[2,3-a]-isoindol-5(9bH)-one

9. 8-chloro-9b-(3-trifluoromethylphenyl)-2,3-dihydro-oxazolo-[2,3-a]-isoindol-5(9bH)-one

10. 6-methoxy-9b-(4-trifluoromethylphenyl)-2,3-dihydrooxazolo-[2,3-a]-isoindol-5(9bH)-one

11. 9b-(4-hydroxypehnyl)-2,3-dihydrooxazolo-[2,3-a]-isoindole-5(9bH)-thione

12. 8-chloro-9b-(3-hydroxyphenyl)-2,3-dihydrooxazolo-[2,3-a]-isoindol-5(9bH)-one

13. 7-methylmercapto-9b-(4-ethoxyphenyl)-2,3-dihydro-oxazolo-[2,3-a]-isoindol-5(9bH)-one

14. 9-methyl-9b-(3-methoxyphenyl)-2,3-dihydrooxazolo-[2,3-a]-isoindol-5-(9bH)-one

15. 8-fluoro-9b-(3-fluorophenyl)-2,3-dihydrooxazolo-[2,3-a]-isoindol-5(9bH)-one

16. 9b-(4-chlorophenyl)-2,3-dihydrooxazolo-[2,3-a]-isoindole-5(9bH)-thione

17. 8-methyl-9b-(3-methylsulphonylphenyl)-2,3-dihydrooxazolo-[2,3-a]-isoindol-5(9bH)-one

18. 8-chloro-9b-phenyl-2,3-dihydrooxazolo-[2,3-a]-isoindol-5(9bH)-one 1-oxide

19. 8-chloro-9b-benzyl-2,3-dihydrooxazolo-[2,3-a]-isoindol-5(9bH)-one

20. 2,2-dimethyl-9b-phenethyl-2,3-dihydrooxazolo-[2,3-a]-isoindol-5(9bH)-one

21. 9b-(3-methylmercaptophenyl)-2,3-dihydrooxazolo-[2,3-a]-isoindol-5(9bH)-one

22. 9b-(3-methylaminophenyl)-2,3-dihydrooxazolo-[2,3-a]-isoindol-5(9bH)-one

23. 9b-(3-azidophenyl)-2,3-dihydrooxazolo-[2,3-a]-isoindol-5(9bH)-one

24. 8-methyl-9b-allyl-2,3-dihydrooxazolo-[2,3-a]-isoindol-5(9bH)-one

25. 8-chloro-9b-(3,5-dimethylphenyl)-2,3-dihydrooxazolo-[2,3-a]-isoindol-5(9bH)-one

26. 8-methyl-9b-(1-naphthyl)-2,3-dihydrooxazolo-[2,3-a]-isoindol-5(9bH)-one

27. 9b-(anthracen-1-yl)-2,3-dihydrooxazolo-[2,3-a]-isoindole-5(9bH)-one

28. 9b-(anthracen-9-yl)-2,3-dihydrooxazolo-[2,3-a]-isoindol-5(9bH)-one

29. 9b-(inden-1-yl)-2,3-dihydrooxazolo-[2,3-a]-5(9bH)-one

30. 9b-(inden-3-yl)-2,3-dihydrooxazolo-[2,3-a]-isoindol-5(9bH)-one

31. 9b-(inden-4-yl)-2,3-dihydrooxazolo-[2,3-a]-isoindole-5(9bH)-thione

32. 9b-(phenanthren-1-yl)-2,3-dihydrooxazolo-[2,3-a]-isoindol-5(9bH)-one

33. 9b-(phenanthren-9-yl)-2,3-dihydrooxazolo-[2,3-a]-isoindol-5(9bH)-one

34. 9b-(cyclohexen-3-yl)-2,3-dihydrooxazolo-[2,3-a]-isoindole-5(9bH)-thione

35. 9b-(2-furyl)-2,3-dihydrooxazolo-[2,3-a]-isoindole-5(9bH)-thione

36. 9b-(3-furyl)-2,3-dihydrooxazolo-[2,3-a]-isoindol-5(9bH)-one

37. 9b-(2-thienyl)-2,3-dihydrooxazolo-[2,3-a]-isoindole-5(9bH)-thione

38. 9b-(3-thienyl)-2,3-dihydrooxazolo-[2,3-a]-isoindol-5(9bH)-one

39. 9b-(pyrimidin-4-yl)-2,3-dihydrooxazolo-[2,3-a]-isoindol-5(9bH)-one

40. 9b-(thiazol-2-yl)-2,3-dihydrooxazolo-[2,3-a]-isoindol-5(9bH)-one

41. 9b-(thiazol-4-yl)-2,3-dihydrooxazolo-[2,3-a]-isoindole-5(9bH)-thione

42. 9b-(indol-3-yl)-2,3-dihydrooxazolo-[2,3-a]-isoindol-5(9bH)-one

43. 9b-(indol-7-yl)-2,3-dihydrooxazolo-[2,3-a]-isoindol-5(9bH)-one

44. 9b-(quinolin-4-yl)-2,3-dihydrooxazolo-[2,3-a]-isoindol-5(9bH)-one

45. 9b-(quinolin-5-yl)-2,3-dihydrooxazolo-[2,3-a]-isoindole-5(9bH)-thione

46. 9b-(benzimidazol-4-yl)-2,3-dihydrooxazolo-[2,3-a]-isoindol-5(9bH)-one

47. 9b-(carbazol-1-yl)-2,3-dihydrooxazolo-[2,3-a]-isoindol-5(9bH)-one

48. 9b-(carbazol-4-yl)-2,3-dihydrooxazolo-[2,3-a]-isoindole-5(9bH)-thione

49. 9b-(phenothiazin-1-yl)-2,3-dihydrooxazolo-[2,3-a]-isoindole-5(9bH)-thione

50. 9b-(phenothiazin-4-yl)-2,3-dihydrooxazolo-[2,3-a]-isoindol-5(9bH)-one

51. 9b-(4-quinazolin-4-yl)-2,3-dihydrooxazolo-[2,3-a]-isoindol-5(9bH)-one

52. 8-chloro-9b-(inden-3-yl)-2,3-dihydrooxazolo-[2,3-a]-isoindol-5(9bH)-one

53. 8-methyl-9b-(isoquinolin-1-yl)-2,3-dihydro-oxazolo-[2,3-a]-isoindole-5(9bH)-thione

54. 9-methoxy-9b-(1-naphthyl)-2,3-dihydrooxazolo-[2,3-a]-isoindol-5(9bH)-one

55. 9b-(cumaron-3-yl)-2,3-dihydrooxazolo-[2,3-a]-isoindol-5(9bH)-one

Compounds of the formula I, in which Y signifies the group $-NR^7$, are especially the following:

1. 8,9b-dimethyl-2,3-dihydroimidazo-[2,1-a]-isoindol-5(9bH)-one

2. 8-chloro-9b-phenyl-2,3-dihydroimidazo-[2,1-a]-isoindol-5(9bH)-one

3. 8-fluoro-9b-(4-methylphenyl)-2,3-dihydroimidazo-[2,1-a]-isoindol-5(9bH)-one

4. 8-chloro-9b-(3-methylphenyl)-2,3-dihydroimidazo-[2,1-a]-isoindol-5(9bH)-one

5. 3-methyl-9b-(4-ethylphenyl)-2,3-dihydroimidazo-[2,1-a]-isoindol-5(9bH)-one

6. 9b-(2,3-dimethylphenyl)-2,3-dihydroimidazo-[2,1-a]-isoindole-5(9bH)-thione

7. 8-chloro-9b-(3,4-dimethylphenyl)-2,3-dihydro-imidazo-[2,1-a]-isoindole-5(9bH)-thione

8. 2-ethyl-9b-(2,5-dimethylphenyl)-2,3-dihydro-imidazo-[2,1-a]-isoindol-5(9bH)-one

9. 8-chloro-9b-(3-trifluoromethylphenyl)-2,3-dihydro-imidazo-[2,1-a]-isoindol-5(9bH)-one

10. 6-methoxy-9b-(4-trifluoromethylphenyl)-2,3-dihydro-imidazo-[2,1-a]-isoindol-5(9bH)-one

11. 9b-(4-hydroxyphenyl)-2,3-dihydroimidazo-[2,1-a]-isoindole-5(9bH)-thione

12. 8-chloro-9b-(3-hydroxyphenyl)-2,3-dihydro-imidazo-[2,1-a]-isoindol-5(9bH)-one

13. 7-methylmercapto-9b-(4-ethoxyphenyl)-2,3-dihydro-imidazo-[2,1-a]-isoindol-5(9bH)-one

14. 9-methyl-9b-(3-methoxyphenyl)-2,3-dihydroimidazo-[2,1-a]-isoindol-5(9bH)-one

15. 8-fluoro-9b-(3-fluorophenyl)-2,3-dihydroimidazo-[2,1-a]-isoindol-5(9bH)-one

16. 9b-(4-chlorophenyl)-2,3-dihydroimidazo-[2,1-a]-isoindole-5(9bH)-thione

17. 8-methyl-9b-(3-methylsulphonylphenyl)-2,3-dihydroimidazo-[2,1-a]-isoindol-5(9bH)-one

18. 8-chloro-9b-phenyl-2,3-dihydroimidazo-[2,1-a]-isoindol-5(9bH)-one 1-oxide

19. 8-chloro-9b-benzyl-2,3-dihydroimidazo-[2,1-a]-isoindol-5(9bH)-one

20. 2,2-dimethyl-9b-phenethyl-2,3-dihydroimidazo-[2,1-a]-isoindol-5(9bH)-one

21. 9b-(3-methylmercaptophenyl)-2,3-dihydroimidazo-[2,1-a]-isoindol-5(9bH)-one

22. 9b-(3-methylaminophenyl)-2,3-dihydroimidazo-[2,1-a]-isoindol-5(9bH)-one

23. 9b-(3-azidophenyl)-2,3-dihydroimidazo-[2,1-a]-isoindol-5(9bH)-one

24. 8-methyl-9b-allyl-2,3-dihydroimidazo-[2,1-a]-isoindol-5(9bH)-one

25. 8-chloro-9b-(3,5-dimethylphenyl)-2,3-dihydroimidazo-[2,1-a]-isoindol-5(9bH)-one

26. 8-methyl-9b-(1-naphthyl)-2,3-dihydroimidazo-[2,1-a]-isoindol-5(9bH)-one

27. 9b-(anthracen-1-yl)-2,3-dihydroimidazo-[2,1-a]-isoindole-5(9bH)-thione

28. 9b-(anthracen-9-yl)-2,3-dihydroimidazo-[2,1-a]-isoindol-5(9bH)-one

29. 9b-(inden-1-yl)-2,3-dihydroimidazo-[2,1-a]-isoindol-5(9bH)-one

30. 9b-(inden-3-yl)-2,3-dihydroimidazo-[2,1-a]-isoindol-5(9BH)-one

31. 9b-(inden-4-yl)-2,3-dihydroimidazo-[2,1-a]-isoindole-5(9bH)-thione

32. 9b-(phenanthren-1-yl)-2,3-dihydroimidazo-[2,1-a]-isoindol-5(9bH)-one

33. 9b-(phenanthren-9-yl)-2,3-dihydroimidazo-[2,1-a]-isoindol-5(9bH)-one

34. 9b-(cyclohexen-3-yl)-2,3-dihydroimidazo-[2,1-a]-isoindole-5(9bH)-thione

35. 9b-(2-furyl)-2,3-dihydroimidazo-[2,1-a]-isoindole-5(9bH)-thione

36. 9b-(3-furyl)-2,3-dihydroimidazo-[2,1-a]-isoindol-5(9bH)-one

37. 9b-(2-thienyl)-2,3-dihydroimidazo-[2,1-a]-isoindole-5(9bH)-thione

38. 9b-(3-thienyl)-2,3-dihydroimidazo-[2,1-a]-isoindol-5(9bH)-one

39. 9b-(pyrimidin-4-yl)-2,3-dihydroimidazo-[2,1-a]-isoindol-5(9bH)-one

40. 9b-(thiazol-2-yl)-2,3-dihydroimidazo-[2,1-a]-isoindol-5(9bH)-one

41. 9b-(thiazol-4-yl)-2,3-dihydroimidazo-[2,1-a]-isoindole-5(9bH)-thione

42. 9b-(indol-3-yl)-2,3-dihydroimidazo-[2,1-a]-isoindol-5(9bH)-one

43. 9b-(indol-7-yl)-2,3-dihydroimidazo-[2,1-a]-isoindol-5(9bH)-one

44. 9b-(quinolin-4-yl)-2,3-dihydroimidazo-[2,1-a]-isoindol-5(9bH)-one

45. 9b-(quinolin-5-yl)-2,3-dihydroimidazo-[2,1-a]-isoindole-5(9bH)-thione

46. 9b-(benzimidazol-4-yl)-2,3-dihydroimidazo-[2,1-a]-isoindol-5(9bH)-one

47. 9b-(carbazol-1-yl)-2,3-dihydroimidazo-[2,1-a]-isoindol-5(9bH)-one

48. 9b-(carbazol-4-yl)-2,3-dihydroimidazo-[2,1-a]-isoindole-5(9bH)-thione

49. 9b-(phenothiazin-1-yl)-2,3-dihydroimidazo-[2,1-a]-isoindole-5(9bH)-thione

50. 9b-(phenothiazin-4-yl)-2,3-dihydroimidazo-[2,1-a]-isoindol-5(9bH)-one

51. 9b-(4-quinazolin-4-yl)-2,3-dihydroimidazo-[2,1-a]-isoindol-5(9bH)-one

52. 8-chloro-9b-(inden-3-yl)-2,3-dihydroimidazo-[2,1-a]-isoindol-5(9bH)-one

53. 8-methyl-9b-(isoquinolin-1-yl)-2,3-dihydro-imidazo-[2,1-a]-isoindole-5(9bH)-thione

54. 9-methoxy-9b-(1-naphthyl)-2,3-dihydroimidazo-[2,1-a]-isoindol-5(9bH)-one

55. 9b-(cumaron-3-yl)-2,3-dihydroimidazo-[2,1-a]-isoindol-5(9bH)-one.

Example 1

9b-(1-Naphthyl)-2,3-dihydrooxazolo-[2,3-a]-isoindol-5(9bH)-one

2.76 g (10 mmol) 2-(1-naphthoyl)-benzoic acid were dissolved in 100 ml xylene and, after addition of 1.22 g (20 mmol) ethanolamine, as well as of a catalytic amount of p-toluenesulphonic acid, heated under reflux for 1 h on a water separator. The solvent was then removed in a vacuum and the residue recrystallised from ethanol. Yield 2.1 g (70% of theory), m.p. 144 - 146°C.

The 2-(1-naphthoyl)-benzoic acid used was prepared by slow dropwise addition of 1-naphthyl magnesium bromide in ether/toluene 4/1 at -10°C to a solution of phthalic acid anhydride in toluene, after 2 hours post-stirring addition of sat. NH_4Cl solution, extraction with ethyl acetate, shaking out of the ethyl ester phase with 2N soda solution and renewed extraction of the acidified soda phase with ethyl acetate. Yield after recrystallisation from ethanol 64% of theory, m.p. 170°C.

The following compounds were prepared analogously to Example 1:

1.1 9b-(anthracen-9-yl)-2,3-dihydrooxazolo-[2,3-a]-isoindol-5(9bH)-one; m.p. 205-206°C; yield 45% from 2-(9-anthracenoyl)-benzoic acid and ethanolamine

1.2 7,8-dichloro-9b-(1-naphthyl)-2,3-dihydrooxazolo-[2,3-a]-isoindol-5(9bH)-one; m.p. 165-172°C; yield: 45%

from 4,5-dichloro-2-benzoylbenzoic acid and ethanolamine

1.3 9b-(2-thienyl)-2,3-dihydrooxazolo-[2,3-a]-isoindol-5(9bH)-one; m.p. 101-104°C

from 2-(2-thienoyl)-benzoic acid and ethanolamine (64% yield)

1.4 9b-(2-furyl)-2,3-dihydrooxazolo-[2,3-a]-isoindol-5(9bH)-one;

from 2-(2-furoyl)-benzoic acid and ethanolamine

1.5 8-methoxy-9b-phenyl-2,3-dihydrooxazolo-[2,3-a]-isoindol-5(9bH)-one;

from 4-methoxy-2-benzoylbenzoic acid and ethanolamine

1.6 8-chloro-9b-phenyl-2,3-dihydrooxazolo-[2,3-a]-isoindol-5(9bH)-one; m.p. 112-114°C,

from 4-chloro-2-benzoylbenzoic acid and ethanolamine (58% yield)

1.7 8-methyl-9b-phenyl-2,3-dihydrooxazolo-[2,3-a]-isoindol-5(9bH)-one; m.p. 103-104°C; yield 60%

from 4-methyl-2-benzoylbenzoic acid and ethanolamine

1.8 8-trifluoromethyl-9b-phenyl-2,3-dihydrooxazolo-[2,3-a]-isoindol-5(9bH)-one;

from 4-trifluoromethyl-2-benzoylbenzoic acid and ethanolamine

1.9 9b-(4-pyridyl)-2,3-dihydrooxazolo-[2,3-a]-isoindol-5(9bH)-one; m.p. 115-118°C.

from 2-(4-pyridoyl)-benzoic acid and ethanolamine (62% yield)

1.10 9b-methyl-2,3-dihydrooxazolo-[2,3-a]-isoindol-5(9bH)-one; oil; yield 61%
from 2-acetylbenzoic acid and ethanolamine

1.11 9b-butyl-2,3-dihydrooxazolo-[2,3-a]-isoindol-5(9bH)-one; oil; yield 53%
from 2-butyrylbenzoic acid and ethanolamine

1.12 9b-phenyl-2,3-dihydrooxazolo-[2,3-a]-isoindol-5(9bH)-one; m.p. 148-150°C,
from 2-benzoylbenzoic acid and ethanolamine (75% yield)

1.13 9b-(4-fluorophenyl)-2,3-dihydrooxazolo-[2,3-a]-isoindol-5(9bH)-one; m.p. 103-104°C; yield 64%
from (4-fluorobenzoyl)-benzoic acid and ethanolamine

1.14 9b-(3-methylphenyl)-2,3-dihydrooxazolo-[2,3-a]-isoindol-5(9bH)-one; m.p. 79-85°C; yield 45%
from 2-(3-methylbenzoyl)-benzoic acid and ethanolamine

1.15 9b-(3-chlorophenyl)-2,3-dihydrooxazolo-[2,3-a]-isoindol-5(9bH)-one; m.p. 95-96°C; yield 72%
from 2-(3-chlorobenzoyl)-benzoic acid and ethanolamine

1.16 9b-(3-methoxyphenyl)-2,3-dihydrooxazolo-[2,3-a]-isoindol-5(9bH)-one; m.p. 120-121°C; yield 62%
from 2-(3-methoxybenzoyl)-benzpic acid and ethanolamine

1.17 9b-(3-trifluorophenyl)-2,3-dihydrooxazolo-[2,3-a]-isoindol-5(9bH)-one; m.p. 97-98°C; yield 46%
from 2-(3-trifluorobenzoyl)-benzoic acid and ethanolamine

1.18 9b-(3,5-dimethylphenyl)-2,3-dihydrooxazolo-[2,3-a]-isoindol-5(9bH)-one;
from 2-(3,5-dimethylbenzoyl)-benzoic acid and ethanolamine

1.19 9b-(3,5-dichlorophenyl)-2,3-dihydrooxazolo-[2,3-a]-isoindol-5(9bH)-one; m.p. 158-159°C; yield 70%
from 2-(3,5-dichlorobenzoyl)-benzoic acid and ethanolamine

1.20 9b-(4-indanyl)-2,3-dihydrooxazolo-[2,3-a]-isoindol-5(9bH)-one; m.p. 153-157°C; yield 39%
from 2-(4-indanoyl)-benzoic acid and ethanolamine

1.21 9b-(5-tetralinyl)-2,3-dihydrooxazolo-[2,3-a]-isoindol-5(9bH)-one;
from 2-(5-tetralinoyl)-benzoic acid and ethanolamine

1.22 9b-(2-benzothiophenyl)-2,3-dihydrooxazolo-[2,3-a]-isoindol-5(9bH)-one;
from 2-(2-benzothiophenoyl)-benzoic acid and ethanolamine

1.23 9b-(2-benzofuranyl)-2,3-dihydrooxazolo-[2,3-a]-isoindol-5(9bH)-one;

from 2-(2-benzofuranoyl)-benzoic acid and ethanolamine

1.24 9b-(3-indolyl)-2,3-dihydrooxazolo-[2,3-a]-isoindol-5(9bH)-one; m.p. 210-213°C; yield 39% from 2-(3-indoloyl)-benzoic acid and ethanolamine

1.25 9b-(4-quinolinyl)-2,3-dihydrooxazolo-[2,3-a]-isoindol-5(9bH)-one;
from 2-(4-quinolinoyl)-benzoic acid and ethanolamine

1.26 9b-(1-isoquinolinyl)-2,3-dihydrooxazolo-[2,3-a]-isoindol-5(9bH)-one;
from 2-(1-isoquinolinoyl)-benzoic acid and ethanolamine

1.27 9b-phenyl-2,3-dihydrooxazolo-[2,3-a]-isoindol-5(9bH)-imine; m.p. 109-111°C; yield 47%
from 2-benzoylbenzonitrile and ethanolamine

1.28 9b-phenyl-3-isopropyl-2,3-dihydrooxazolo-[2,3-a]-isoindol-5(9bH)-one; oil
$[\alpha]_D^{20}$ = +248.7 ($CHCl_3$)
from 2-benzoylbenzoic acid and S-(+)-valinol (73% yield)

1.29 (+)- and (-)-9b-phenyl-2-methyl-2,3-dihydro-oxazolo[2,3-a]-isoindol-5(9bH)-one;
m.p. 147°C, $[\alpha]_D^{20}$ = +137 ($CHCl_3$) and
m.p. 154°C., $[\alpha]_D^{20}$ = -263 ($CHCl_3$),
from 2-benzoylbenzoic acid and R-(-)-1-amino-2-

propanol after separation on cellulose triacetate with methanol/water 7:3

1.30 (+)- and (-)-9b-phenyl-2-methyl-2,3-dihydro-oxazolo-[2,3-a]-isoindol-5(9bH)-one; m.p. 154°C, $[\alpha]_D^{20}$ = +261.1 ($CHCl_3$) and m.p. 147°C, $[\alpha]_D^{20}$ = 137 ($CHCl_3$) from 2-benzoylbenzoic acid and S-(+)-1-amino-2-propanol after separation on RP 18 with methanol/water 6:4

1.31 9b-phenyl-2,3-dimethyl-2,3-dihydrooxazolo-[2,3-a]-isoindol-5(9bH)-one; m.p. 76°C, from 2-benzoylbenzoic acid and (+/-)-2-amino-3-butanol

1.32 (+)-9b-phenyl-3-methyl-2,3-dihydrooxazolo-[2,3-a]-isoindol-5(9bH)-one; m.p. 140-141°C; $[\alpha]_D^{20}$ = +313.3 ($CHCl_3$) from 2-benzoylbenzoic acid and S-(+)-2-amino-1-propanol

1.33 (-)-9b-phenyl-3-methyl-2,3-dihydrooxazolo-[2,3-a]-isoindol-5(9bH)-one; m.p. 142-143°C. $[\alpha]_D^{20}$ = -318.5 ($CHCl_3$) from 2-benzoylbenzoic acid and R-(-)-2-amino-1-propanol

1.34 9b-phenyl-2,2-dimethyl-2,3-dihydrooxazolo-[2,3-a]-isoindol-5(9bH)-one; m.p. 149°C from 2-benzoylbenzoic acid and 3-amino-2-methyl-2-propanol (85% yield)

1.35 (+)-9b-phenyl-3-methoxycarbonyl-2,3-dihydro-oxazolo-/2,3-a/-isoindol-5(9bH)-one; m.p. from 2-benzoylbenzoic acid and L-serine methyl ester

1.36 9b-phenyl-2,3-dihydrooxazolo-/2,3-a/-isoindole-5(9bH)-one; from 2-benzoylbenzonitrile and ethanolamine

Example 2

9b-Phenyl-2,3-dihydrooxazolo-/2,3-a/-isoindole-5(9bH)-thione

1.9 g (7.5 mmol) 9b-phenyl-2,3-dihydrooxazolo-/2,3-a/-isoindolin-5(9bH)-one (Example 1.12) in 100 ml abs. dioxane were mixed with 3.8 g (9.4 mmol) Lawesson's reagent /2,4-bis-(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane-2,4-disulphide/ and stirred for 5 h at 60°C (TLC control).

After cooling, it was filtered off from precipitate, the filtrate evaporated in a vacuum and the residue purified by flash column chromatography with heptane/methyl ethyl ketone 6/1 as eluent.

Example 3

Enantiomer separation of rac-8-chloro-9b-phenyl-2,3-dihydrooxazolo-/2,3-a/-isoindol-5(9bH)-one (Example 1.6) on cellulose triacetate

For the separation of the antipodes, 200 mg of the racemate were dissolved in 15 ml ethanol, applied to a column with 50 mm internal diameter and 300 mm length (corresponding to 250 g cellulose triacetate,

15-25 grain size, Merck 16326) and eluted with ethanol (flow 7.5 ml/min, about 1.5 bar).

	Peak I	Peak II
UV detection [nm]	254	254
$[\alpha]_D^{20}$:	+114.8	-115.2
m.p. [°C] :	89-91	89-91

The enantiomers were recrystallised from ethanol. + Enantiomer purity according to HPLC in each case > 99.6% ee.

Example 4

9b-Phenyl-2,3-dihydroimidazo-[2,1-a]-isoindol-5(9bH)-one

5.0 g (22 mmol) 2-benzoylbenzoic acid were dissolved in 100 ml toluene and, after addition of 6.6 g (110 mmol) ethylenediamine, as well as of a catalytic amount of p-toluenesulphonic acid, heated under reflux for 12 h on a water separator. The solvent was then removed in a vacuum and the residue recrystallised from ethanol. Yield 3.5 g (63% of theory), m.p. 152-154°C.

Example 5

1-Acetyl-9b-phenyl-2,3-dihydroimidazo-[2,1-a]-isoindol-5(9bH)-one

1 g (4 mmol) of the compound obtained in Example 4 were stirred with 10 ml acetic acid anhydride for 8 h at room temperature. One pours on to water, filters off with suction the residue which precipitates out and washes the crystals with ether. Yield: 1.1 g

(92% of theory), m.p. 171-173°C.

Example 6

1-Methyl-9b-phenyl-2,3-dihydroimidazo-/2,1-a7-isoindol-5(9bH)-one

1 g (4 mmol) of the compound obtained in Example 4 were dissolved in 5 ml DMF and mixed with 0.5 ml methyl iodide and 0.13 g NaH (100 percent). After four hours stirring, 0.5 ml methyl iodide and 0.13 g NaH (100 percent) were again added thereto. After a further 2 h, the reaction solution was added to water, extracted with ethyl acetate, dried and the solvent evaporated off in a vacuum. After column chromatography on silica gel (elution agent: ethyl acetate/isohexane, 1:2), one collects the desired fractions and crystallises the residue from isohexane and a few drops of ethanol. Yield: 0.59 g (56% of theory), m.p. 119-121°C.

Example 7

Inhibition of HIV reverse transcriptase (RT) by derivatives of 9b-phenyl-2,3-dihydrooxazolo-/2,3-a7-isoindol-5(9bH)-one and 9b-phenyl-2,3-dihydroimidazo-/2,1-a7-isoindol-5(9bH)-one

The screening test system contains the purified RT from HIV-1, which was expressed by gene-technological methods in E. coli, as well as the components of the initiation complex, such as the in vitro transcripts of the HIV-LTR's with the neighbouring primer binding site as template and an 18mer oligo-

nucleotide complementary to the primer binding site as primer. There was measured the /-^{3}H/-thymidine-5'-triphosphate incorporation by counting in the β-counter. In the following Table is given the IC50 value for the investigated compounds. This value corresponds to that concentration of the test substance which brings about an inhibition of the reverse transcriptase activity of 50%.

Results:

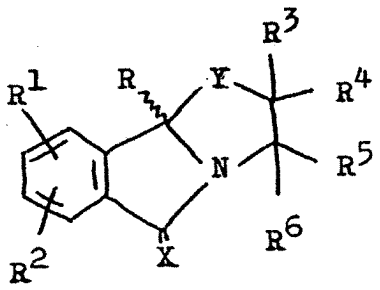
substance	inhibition of the HIV-RT IC_{50} /M/
9b-phenyl-2,3-dihydrooxazolo-/2,3-a/-isoindol-5(9bH)-one	6.1×10^{-6}
7,8-dichloro-9b-phenyl-2,3-dihydrooxazolo-/2,3-a/-isoindol-5(9bH)-one	14.1×10^{-6}
9b-(1-naphthyl)-2,3-dihydrooxazolo-/2,3-a/-isoindol-5-(9bH)-one	1.8×10^{-6}
9b-(3-methylphenyl)-2,3-dihydrooxazolo-/2,3-a/-isoindol-5(9bH)-one	7.9×10^{-6}
8-chloro-9b-phenyl-2,3-dihydrooxazolo-/2,3-a/-isoindol-5(9bH)-one	5.7×10^{-6}
9b-(3-chlorophenyl)-2,3-dihydrooxazolo-/2,3-a/-isoindol-5(9bH)-one	2.1×10^{-6}

substance	inhibition of the HIV-RT IC_{50} /M/
9b-(3,5-dichlorophenyl)-2,3-dihydrooxazolo-/2,3-a/isoindol-5(9bH)-one	2.2×10^{-6}
9b-(3-indolyl)-2,3-dihydro-oxazolo-/2,3-a/-isoindol-5(9bH)-one	7.3×10^{-6}

Summary

The present invention concerns the use of oxazolo-[2,3-a]-isoindole and imidazo-[2,1-a]-isoindole derivatives as antiviral medicaments, as well as new optically-active derivatives, as well as new oxazolo-[2,3-a]-isoindole derivatives, processes for their preparation and medicaments which contain these compounds.

The subject of the invention is especially the use of oxazolo-[2,3-a]-isoindole and imidazo-[2,1-a]-isoindole derivatives of the general formula I



(I),

for the preparation of medicaments with antiviral action, whereby X can be an oxygen or sulphur atom, the imino group =NH or an =N-C_1-C_5-alkylimino group, Y can be an oxygen atom or the group NR^7, whereby R^7 signifies a hydrogen atom or a C_1-C_6-alkyl or C_1-C_6-acyl radical, R signifies a hydrogen atom, a straight-chained or branched, saturated or unsaturated aliphatic radical with 1 - 9 C-atoms, which can be substituted by phenyl, or a phenyl ring which is possibly substituted one or more times,

or represents a carbocyclic or heterocyclic ring, R^1, R^2 signify a hydrogen atom, a straight-chained or branched, saturated or unsaturated aliphatic radical with 1-6 C-atoms, R^3 - R^6 hydrogen, C_1-C_6-alkyl, C_1-C_6-alkoxy, C_1-C_6-alkylmercapto, amino, C_1-C_6-alkylamino, di-C_1-C_6-alkylamino, halogen, cyano, hydroxyl, carboxyl, aminocarbonyl, substituted aminocarbonyl or C_1-C_6-alkoxycarbonyl, as well as their tautomers, enantiomers, diseastereomers and physiologically compatible salts.

Amended page 5 of the German text.

aminocarbonyl, C_1-C_6-alkylaminocarbonyl or di-C_1-C_6-alkylaminocarbonyl, R^4, R^5, R^6 have the same meaning as R^3, whereby the radicals R^3, R^4, R^5 and R^6, independently of one another, can be the same or different, as well as their tautomers, enantiomers, diastereomers and physiologically compatible salts.

For the case that Y is an oxygen atom, R^1 and R^2 do not simultaneously signify hydrogen atoms and R^1 or R^2 do not signify lower alkyl, alkoxy, amino, halogen, nitro and trifluoromethyl, it is a question of new oxazolo-[2,3-a]-isoindole derivatives which are also the subject of the present invention.

The compounds of the formula I have hitherto only been known in the form of their racemates. It has now been shown that the optically-active derivatives possess a higher effectiveness than the corresponding racemic mixtures so that the present invention also refers to the new R- and S-enantiomers.

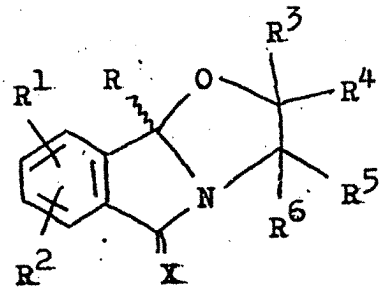
The compounds of the formula I display valuable pharmacological properties. In particular, they are suitable for the therapy and prophylaxis of infections which are caused by DNA viruses, such as e.g. herpes simplex virus, cytomegalovirus, papillomaviruses, the varicella zoster virus or Epstein-Barr virus or RNA viruses, such as togaviruses or especially retroviruses, such as the oncoviruses HTLV-L and II,

as well as the lentiviruses and human immune deficiency virus HIV-1 and -2.

The compounds of the formula I appear to be especially suitable for the treatment of the clinical manifestations of the retroviral HIV infection in humans, as well as of the persistent general lymphadenopathy (PGL), the advanced stage of the AIDS-related complex (ARC) and the clinically complete picture of AIDS.

Amended pages 35 and 36 of the German text

5. Oxazolo-[2,3-a]-isoindole derivatives of the general formula Ia



(Ia)

in which X can be an oxygen or sulphur atom, the imino group =NH or an =N-C_1-C_5-alkylimino group, R signifies a hydrogen atom, a straight-chained or branched, saturated or unsaturated aliphatic radical with 1 - 9 C-atoms, which can be substituted by phenyl, or a C_1-C_6-alkoxy-C_1-C_6-alkyl or C_1-C_6-alkylmercapto-C_1-C_6-alkyl radical, or signifies a phenyl ring which is possibly substituted one or more times by C_1-C_6-alkyl, C_1-C_6-alkoxy, C_1-C_6-alkylmercapto, C_1-C_6alkylsulphinyl, C_1-C_6-alkylsulphonyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl, C_2-C_6-alkenyloxy, C_2-C_6-alkenylmercapto, C_2-C_6-alkynyloxy, C_2-C_6-alkylamino, di-C_1-C_6-alkylamino, C_1-C_6-alkylcarbonylamino, C_1-C_6-alkylaminocarbonyl, C_1-C_6-alkoxycarbonyl, hydroxyl, benzyloxy, phenylmercapto, phenyloxy, nitro, cyano, halogen, trifluoromethyl, azido, formylamino, carboxyl or phenyl, or signifies a mono-, bi- or tricyclic carbocyclic ring with 7 - 15 C-atoms or a heterocyclic mono-, bi- or tricyclic ring system

with, in each case, 5 or 6 ring atoms and, per ring system, can contain 1 - 4 or 1 - 5 heteroatoms, respectively, whereby the heteroatoms are nitrogen, sulphur or oxygen, R^1 signifies a straight-chained or branched unsaturated aliphatic radical with up to 6 C-atoms, C_1-C_6-alkylmercapto, C_1-C_6-alkylsulphinyl, C_1-C_6-alkylsulphonyl, C_1-C_6-alkylamino, di-C_1-C_6-alkylamino, sulphonamido, C_1-C_6-alkoxycarbonyl, carboxyl, hydroxyl, cyano, azido, phenyl or benzyloxy, R^2 signifies a hydrogen atom or has the same meaning as R^1, R^3 signifies hydrogen, C_1-C_6-alkyl, C_1-C_6-alkoxy, C_1-C_6-alkylmercapto, amino, C_1-C_6-alkylamino, di-C_1-C_6-alkylamino, halogen, cyano, hydroxyl, carboxyl, C_1-C_6-alkoxycarbonyl, aminocarbonyl, C_1-C_6-alkylamino-carbonyl or di-C_1-C_6-alkylaminocarbonyl, R^4, R^5, R^6 have the same meaning as R^3, whereby the radicals R^3, R^4, R^5 and R^6, independently of one another, can be the same or different, as well as their tautomers, enantiomers, diastereomers and physiologically compatible salts.

6. R- and S-oxazolo-/3,3-a/-isoindole and R- and S-imidazo-/3,1-a/-

Amended pages 38 and 39 of the German text

signifies a mono-, bi- or tricyclic carbocyclic ring with 7 - 15 C-atoms or a heterocyclic mono-, bi- or tricyclic ring system with, in each case, 5 or 6 ring atoms and, per ring system, can contain 1 - 4 or 1 - 5 heteroatoms, respectively, whereby the heteroatoms are nitrogen, sulphur or oxygen, R^1 signifies a hydrogen atom, a straight-chained or branched, saturated or unsaturated aliphatic radical with 1 - 6 C-atoms or C_1-C_6-alkoxy, C_1-C_6-alkylmercapto, C_1-C_6-alkylsulphinyl, C_1-C_6-alkylsulphonyl, amino, C_1-C_6-alkylamino, di-C_1-C_6-alkylamino, sulphonamido, C_1-C_6-alkoxycarbonyl, trifluoromethyl, carboxyl, halogen, hydroxyl, nitro, cyano, azido, phenyl or benzyloxy, R^2 has the same meaning as R^1, whereby the radicals R^1 and R^2, independently of one another, can be the same or different, R^3 signifies hydrogen, C_1-C_6-alkyl, C_1-C_6-alkoxy, C_1-C_6-alkylmercapto, amino, C_1-C_6-alkylamino, di-C_1-C_6-alkylamino, halogen, cyano, hydroxyl, carboxyl, C_1-C_6-alkoxycarbonyl, aminocarbonyl, C_1-C_6-alkylaminocarbonyl or di-C_1-C_6-alkylaminocarbonyl, R^4, R^5, R^6 have the same meaning as R^3, whereby the radicals R^3, R^4, R^5 and R^6, independently of one another, can be the same or different, as well as their tautomers, diastereomers and physiologically compatible salts.

7. Medicaments containing at least one compound of the formula I or Ia according to claim 5 or 6,

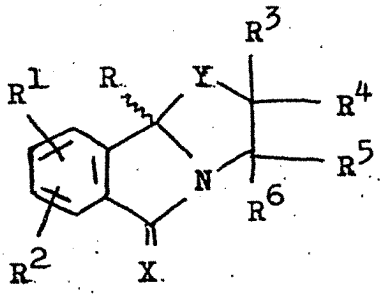
besides pharmacologically compatible adjuvant or carrier materials.

8. Use of compounds of the formula I or Ia according to claim 5 or 6 for the preparation of medicaments for the treatment of viral or retroviral infections or of diseases caused by these infections, such as AIDS or ARC.

9. Process for the preparation of medicaments containing at least one compound of the formula I or Ia according to claim 5 or 6, besides usual carrier or adjuvant materials, characterised in that one mixes a compound of the formula I or Ia with the carrier or adjuvant materials and works up to appropriate forms of administration.

Patent Claims

1. Use of oxazolo-[2,3-a]-isoindole and imidazo-[2,1-a]-isoindole derivatives of the general formula I



(I),

for the preparation of medicaments with antiviral action, whereby X can be an oxygen or sulphur atom, the imino group =NH or an =N-C_1-C_5-alkylimino group, Y can be an oxygen atom or the group NR^7, whereby R^7 signifies a hydrogen atom or a C_1-C_6-alkyl or C_1-C_6-acyl radical, R signifies a hydrogen atom, a straight-chained or branched, saturated or unsaturated aliphatic radical with 1-9 C-atoms, which can be substituted by phenyl, or a C_1-C_6-alkoxy-C_1-C_6-alkyl or C_1-C_6-alkylmercapto-C_1-C_6-alkyl radical or signifies a phenyl ring which is possibly substituted one or more times by C_1-C_6-alkyl, C_1-C_6-alkoxy, C_1-C_6-alkylmercapto, C_1-C_6-alkylsulphinyl, C_1-C_6-alkylsulphonyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl, C_2-C_6-alkenyloxy, C_2-C_6-alkenylmercapto, C_2-C_6-alkynyloxy, C_2-C_6-alkynylmercapto, amino, C_1-C_6-alkylamino, di-C_1-C_6-alkylamino, C_1-C_6-alkylcarbonylamino, C_1-C_6-alkylaminocarbonyl, C_1-C_6-alkoxycarbonyl, hydroxyl,

benzyloxy, phenylmercapto, phenyloxy, nitro, cyano, halogen, trifluoromethyl, azido, formylamino, carboxyl or phenyl, or a mono-, bi- or tricyclic carbocyclic ring with 7 - 15 C-atoms or a heterocyclic mono-, bi- or tricyclic ring system with, in each case, 5 or 6 ring atoms and, per ring system, can contains 1 - 4 or 1 - 5 heteroatoms, respectively, whereby the heteroatoms are nitrogen, sulphur or oxygen, R^1 signifies a hydrogen atom, a straight-chained or branched, saturated or unsaturated aliphatic radical with 1 - 6 C-atoms or C_1-C_6-alkoxy, C_1-C_6-alkylmercapto, C_1-C_6-alkylsulphinyl, C_1-C_6-alkylsulphonyl, amino, C_1-C_6-alkylamino, di-C_1-C_6-alkylamino, sulphonamido, C_1-C_6-alkoxycarbonyl, trifluoromethyl, carboxyl, halogen, hydroxyl, nitro, cyano, azido, phenyl, or benzyloxy, R^2 has the same meaning as R^1, whereby the radicals R^1 and R^2, independently of one another, can be the same or different, R^3 signifies hydrogen, C_1-C_6-alkyl, C_1-C_6-alkoxy, C_1-C_6-alkylmercapto, amino, C_1-C_6-alkylamino, di-C_1-C_6-alkylamino, halogen, cyano, hydroxyl, carboxyl, C_1-C_6-alkoxycarbonyl, aminocarbonyl, C_1-C_6-alkylaminocarbonyl or di-C_1-C_6-alkylaminocarbonyl, R^4, R^5, R^6 have the same meaning as R^3, whereby the radicals R^3, R^4, R^5 and R^6, independently of one another, can be the same or different, as well as their tauromers, enantiomers, diastereomers and physiologically compatible salts.

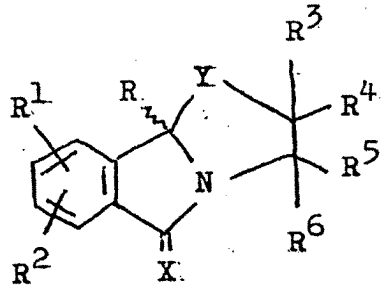
2. Use according to claim 1, characterised in that R signifies a carbocyclic ring with 7 - 15 C-atoms selected from the group naphthyl, anthracenyl, phenanthrenyl, fluorenyl, indenyl, indanyl, acenaphthylenyl, norbornyl, adamantyl ring or a C_3-C_7-cycloalkyl or C_5-C_8-cycloalkenyl group, whereby these can be partly hydrogenated or fully hydrogenated.

3. Use according to claim 1, characterised in that R signifies a heterocyclic mono-, bi- or tricyclic ring selected from the group pyridinyl, pyrimidinyl, pyridazinyl, pyrazinyl, triazinyl, pyrrolyl, pyrazolyl, imidazolyl, triazolyl, thiazolyl, oxazolyl, isoxazolyl, oxadiazolyl, furazanyl, furanyl, thiophenyl, indolyl, quinolinyl, isoquinolinyl, cumaronyl, thionaphthenyl, benzoxazolyl, benzthiazolyl, indazolyl, benzimidazolyl, benztriazolyl, chromenyl, phthalazinyl, quinazolinyl, quinoxalinyl, methylenedioxybenzolyl, carbazolyl, acridinyl, phenoxazinyl, phenothiazinyl, phenazinyl or purine group, whereby the heterocycles can be partly or completely hydrogenated.

4. Use according to claim 1, characterised in that X signifies an oxygen or sulphur atom and Y signifies an oxygen atom or $-NR^7$, whereby R^7 can be hydrogen or C_1-C_6-alkyl or C_1-C_6-acyl radical and R signifies unsubstituted phenyl or phenyl substituted once or twice by C_1-C_6-alkyl, C_1-C_6-alkoxy, C_1-C_6-alkylmercapto, C_1-C_6-alkylsulphinyl, C_1-C_6-alkylsulphonyl,

C_2-C_6-alkenyl, C_2-C_6-alkynyl, C_3-C_6-alkenyloxy, C_1-C_6-alkylamino, C_1-C_6-dialkylamino, C_1-C_6-alkylcarbonylamino, C_1-C_6-alkylaminocarbonyl, C_1-C_6-alkoxycarbonyl, amino, hydroxyl, nitro, azido, trifluoromethyl, cyano or halogen, or signifies biphenyl, naphthyl, anthracenyl, indenyl, fluorenyl, acenaphthylenyl, phenanthrenyl, norbornyl, adamantyl, C_3-C_6-cycloalkyl, C_5-C_8-cycloalkenyl, or signifies pyrrolyl, imidazolyl, furanyl, thiophenyl, pyridinyl, pyrimididinyl, thiazolyl, triazinyl, indolyl, quinolinyl, isoquinolinyl, cumaronyl, thionaphthenyl, benzimidazolyl, quinazolinyl, methylenedioxybenzolyl, ethylenedioxybenzolyl, carbazolyl, acridinyl or phenothiazinyl, and R^1 and R^2 signify hydrogen, C_1-C_6-alkyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl, C_1-C_6-alkoxy, C_1-C_6-alkylmercapto, C_1-C_6-alkylamino, C_1-C_6-alkoxycarbonyl, trifluoromethyl, amino, halogen, hydroxyl, cyano and azido, R^3, R^4, R^5 and R^6 signify hydrogen, C_1-C_6-alkyl, C_1-C_6-alkoxy, C_1-C_6-alkylmercapto, carboxyl, C_1-C_6-alkoxycarbonyl, halogen, cyano and hydroxyl.

5. Oxazolo-[2,3-a]-isoindole derivatives of the general formula I

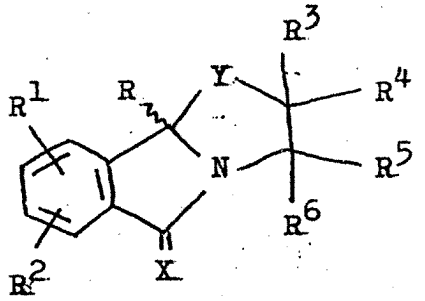


(I),

in which X can be an oxygen or sulphur atom, the imino group =NH or an =N-C_1-C_5-alkylimino group, Y signifies an oxygen atom, R signifies a hydrogen atom, a straight-chained or branched, saturated or unsaturated aliphatic radical with 1 - 9 C-atoms, which can be substituted by phenyl, or a C_1-C_6-alkoxy-C_1-C_6-alkyl or C_1-C_6-alkylmercapto-C_1-C_6-alkyl radical, or signifies a phenyl ring which is possibly substituted one or more times by C_1-C_6-alkyl, C_1-C_6-alkoxy, C_1-C_6-alkylmercapto, C_1-C_6-alkylsulphinyl, C_1-C_6-alkylsulphonyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl, C_2-C_6-alkenyloxy, C_2-C_6-alkenylmercapto, C_2-C_6-alkynyloxy, C_2-C_6-alkynylmercapto, amino, C_1-C_6-alkylamino, di-C_1-C_6-alkylamino, C_1-C_6-alkylcarbonylamino, C_1-C_6-alkylaminocarbonyl, C_1-C_6-alkoxycarbonyl, hydroxyl, benzyloxy, phenylmercapto, phenyloxy, nitro, cyano, halogen, trifluoromethyl, azido, formylamino, carboxyl or phenyl, or signifies a mono-, bi- or tricyclic carbocyclic ring with 7 - 15 C-atoms or a heterocyclic mono-, bi- or tricyclic ring system with, in each case, 5 or 6 ring atoms and, per ring

system, can contain 1 - 4 or 1 - 5 heteroatoms, respectively, whereby the heteroatoms are nitrogen, sulphur or oxygen, R^1 signifies a straight-chained or branched, saturated or unsaturated aliphatic radical with 1 - 6 C-atoms or C_1-C_6-alkoxy, C_1-C_6-alkylmercapto, C_1-C_6-alkylsulphinyl, C_1-C_6-alkylsulphonyl, amino, C_1-C_6-alkylamino, di-C_1-C_6-alkylamino, sulphonamido, C_1-C_6-alkoxycarbonyl, trifluoromethyl, carboxyl, halogen, hydroxyl, nitro, cyano, azido, phenyl or benzyloxy, R^2 signifies a hydrogen atom or has the same meaning as R^1, R^3 signifies hydrogen, C_1-C_6-alkyl, C_1-C_6-alkoxy, C_1-C_6-alkylmercapto, amino, C_1-C_6-alkylamino, di-C_1-C_6-alkylamino, halogen, cyano, hydroxyl, carboxyl, C_1-C_6-alkoxycarbonyl, aminocarbonyl, C_1-C_6-alkylaminocarbonyl or di-C_1-C_6-alkylaminocarbonyl, R^4, R^5, R^6 have the same meaning as R^3, whereby the radicals R^3, R^4, R^5 and R^6, independently of one another, can be the same or different, as well as their tautomers, enantiomers, diastereomers and physiologically compatible salts.

6. R- and S-oxazolo-/2,3-a/-isoindole and imidazo-/2,1-a/-isoindole derivatives of the general formula I



(I),

in which X can be an oxygen or sulphur atom, the imino group =NH or an =N-C_1-C_5-alkylimino group, Y can be an oxygen atom or the group NR^7, whereby R^7 signifies a hydrogen atom or a C_1-C_6-alkyl or C_1-C_6-acyl radical, R signifies a hydrogen atom, a straight-chained or branched, saturated or unsaturated aliphatic radical with 1 - 9 C-atoms, which can be substituted by phenyl, or a C_1-C_6-alkoxy-C_1-C_6-alkyl or C_1-C_6-alkylmercapto-C_1-C_6-alkyl radical or signifies a phenyl ring which is possibly substituted one or more times by C_1-C_6-alkyl, C_1-C_6-alkoxy, C_1-C_6-alkylmercapto, C_1-C_6-alkylsulphinyl, C_1-C_6-alkylsulphonyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl, C_2-C_6-alkenyloxy, C_2-C_6-alkenylmercapto, C_2-C_6-alkynyloxy, C_2-C_6-alkynylmercapto, amino, C_1-C_6-alkylamino, di-C_1-C_6-alkylamino, C_1-C_6-alkylcarbonylamino, C_1-C_6-alkylaminocarbonyl, C_1-C_6-alkoxycarbonyl, hydroxyl, benzyloxy, phenylmercapto, phenyloxy, nitro, cyano, halogen, trifluoromethyl, azido, formylamino, carboxyl or phenyl, or a mono-, bi- or tricyclic carbocyclic ring with 7 - 15 C-atoms or a heterocyclic mono-,

bi- or tricyclic ring system with, in each case, 5 or 6 ring atoms and, per ring system, can contain 1 - 4 or 1 - 5 heteroatoms, respectively, whereby the heteroatoms are nitrogen, sulphur or oxygen, R^1 signifies a hydrogen atom, a straight-chained or branched, saturated or unsaturated aliphatic radical with 1 - 6 C-atoms or C_1-C_6-alkoxy, C_1-C_6-alkylmercapto, C_1-C_6-alkylsulphinyl, C_1-C_6-alkylsulphonyl, amino, C_1-C_6-alkylamino, di-C_1-C_6-alkylamino, sulphonamido, C_1-C_6-alkoxycarbonyl, trifluoromethyl, carboxyl, halogen, hydroxyl, nitro, cyano, azido, phenyl or benzyloxy, R^2 has the same meaning as R^1, whereby the radicals R^1 and R^2, independently of one another, can be the same or different, R^3 signifies hydrogen, C_1-C_6-alkyl, C_1-C_6-alkoxy, C_1-C_6-alkylmercapto, amino, C_1-C_6-alkylamino, di-C_1-C_6-alkylamino, halogen, cyano, hydroxyl, carboxyl, C_1-C_6-alkoxycarbonyl, aminocarbonyl, C_1-C_6-alkylaminocarbonyl or di-C_1-C_6-alkylaminocarbonyl, R^4, R^5, R^6 have the same meaning as R^3, whereby the radicals R^3, R^4, R^5 and R^6, independently of one another, can be the same or different, as well as their tautomers, diastereomers and physiologically compatible salts.

7. Medicaments containing at least one compound of the formula I according to claim 5 or 6, besides pharmacologically compatible adjuvant and carrier materials.

8. Use of compounds of the formula I according to claim 5 or 6 for the preparation of medicaments for the treatment of viral or retroviral infections or of diseases caused by these infections.

9. Process for the production of medicaments containing at least one compound of the formula I according to claim 5 or 6, besides pharmaceutically usual carrier and adjuvant materials, characterised in that one mixes a compound of the formula I with the carrier or adjuvant materials and works up to appropriate forms of administration.

Q44471

SUBSTITUTE

REMPLACEMENT

SECTION is not Present

Cette Section est Absente